REMARKS

Claim 1 is pending in this application. Claim 1 has been rejected. Reconsideration is respectfully requested in light of the following remarks.

I. Rejection of Claims Under 35 U.S.C. 112, First Paragraph

Claim 1 has been rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The Examiner suggests that the claim contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Specifically, the Examiner suggests that the term "into the spinal cord but not the brain" is a concept that was not present in the specification as originally filed and that any negative limitation or exclusionary proviso must have basis in the original disclosure. Applicants respectfully disagree with the Examiner's conclusions.

As discussed in the previous reply to the Interview Summary dated October 16, 2007, and as explained in detail in the Office

Action response filed September 19, 2007, the basis for the amended claim 1 language "intrathecally into the spinal cord but not into the brain" is the knowledge of one of skill at the time the application was filed and as such is not required to be explicitly taught in the specification as filed. MPEP 2163 states "What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail." (Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d at 1384, 231 USPQ at 94). Further MPEP 2163 states that "If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate written description requirement is met." (Vas-Cath, 935 F.2d at 1563, 19 USPQ2d at 1116; Martin v. Johnson, 454 F.2d 746, 751, 172 USPQ 391, 395 (CCPA 1972)). Therefore, contrary to the Examiner's assertion in the Office Action at page 3, there is no need to incorporate by reference the Human Anatomy and Physiology textbook because it would have been known to one of skill in the art. Apparently, the Examiner has failed to consider that one of ordinary skill in the art would have the understanding of the difference of intrathecal versus

intraventricular administration wherein intrathecal administration would by definition result in injection of drug "into the spinal cord but not into brain". This was acknowledged in the telephone interview held on October 2, 2007, and at that time the Examiner indicated that the claim was allowable because this was textbook knowledge.

Accordingly, claim 1 meets the requirements of 35 U.S.C. 112, first paragraph based on the knowledge of one of skill in the art at the time the application was filed, which was evidenced by teachings found in textbooks available to one of skill at the time the application was filed. Withdrawal of this rejection is therefore respectfully requested.

II. Rejection of Claims Under 35 U.S.C. 103(a)

Claim 1 has been rejected under 35 U.S.C. 103(a) as being unpatentable over Chamberlain et al. (1998) and Biomethodology of the Rat (http://research.uiowa.edu/animal/ print. php? get+rat). The Examiner has suggested that Chamberlain et al. teach intraventricular administration of methotrexate at a dose of 2 mg daily (40 mg total dose) to patients with leptomenigeal metastases presenting with radiculopathy, and that the method of

administering intrathecally would overlap with this method. Further, the Examiner suggests that the reference on Biomethodology of the Rat teaches that a rat weighs about 250 g and thus the 1 mg/kg dose of the present invention would equate to about 0.8 mg given to a rat. Therefore, the Examiner suggests these references teach the limitations of claim 1. Further, the Examiner suggests that it is routine to "dramatically vary dosage to obtain data on parameters such as toxicity" and thus it would have been obvious to use methotrexate in a dose of 1 mg/kg. As discussed in detail in the previous responses and during the telephone interview, Applicants respectfully disagree with the Examiner's conclusions regarding the cited references.

The Examiner has made several errors not only in statements about doses but also in reasoning regarding basic principles of pharmacology and dose selection for drugs used to treat pain. First, with regard to the teachings of dose and the extrapolation of dose from the teachings of the specification as filed to compare that dose to the teachings of Chamberlain et al., Applicants respectfully disagree with the Examiner's arguments regarding dose extrapolation from mg/kg body weight

doses to mg doses, regardless of body weight. It is a general principle of pharmacology that if an effective dose is taught to be a dose in mg/kg body weight, then in order to extrapolate the dosing from a rat, the species taught in the specification as filed, to a dose that might be used in humans, the species of the Chamberlain et al. reference, the dose extrapolation would be done based on consideration of the difference in body weights, not by ignoring the body weight differences as has been suggested by the Examiner. The contrary is also true. One of skill in the art would never extrapolate from a mg dose in humans to a mg dose in rats without first correcting the mg dose for body weight in humans. This is because of the large difference in size of a human versus a rat. If 2 mg is safe in a very large species (man), that dose could be lethal to a rat, a much smaller species. Instead, dosing would be done by first correcting for body weight. In other words, a 2 mg dose in humans would be 2 mg divided by 60-70 kg body weight which is 0.029 to 0.033 mg/kg/day, a dose much lower than 1 mg/kg as now claimed. The reverse is also true. One of skill would never take a 1 mg/kg dose in a rat and assume that that dose in mg, about 0.8 mg to the rat, would have efficacy in a human based on

the large difference in body size of the human as compared to the rat. The Examiner is totally mistaken in suggesting that one of skill in the art would ignore well-established principles of dose extrapolation and ignore the differences in body size when extrapolating from a rat to humans or even the reverse extrapolating from humans down to rats (as the Examiner is doing in the instant case). In the Office Action, the Examiner has incorrectly described a calculation at page 5. The Examiner states:

> "The claim states that dosages of 1 mg/kg are to be administered, but does not state the frequency of the administration. In Biomethodology of the Rat (U) the weight of a laboratory rat is from about 250 grams to about 800 grams. To convert this weight to a dose that fits the claim, an 800 gram rat would receive about 0.8 mg of methotrexate."

This is an incorrect calculation. 1 mg/kg given to a 800 gram rat is 1 mg/kg divided by 0.8 kg (800 grams) which gives a dose of 1.25 mg NOT 0.8 mg. However, the Examiner has also missed an important point in dose extrapolation. If Chamberlain is teaching use of 2 mg per day in a human, that is NOT simply 2 mg in a rat. This is because of the level of toxicity that would

be expected in giving the same dose to a rat as is used in a human. Rats would be receiving a dose that was much too high based on the size of the animal (800 grams for a rat versus 60 to 70 kg for humans).

The Examiner goes on to state that methotrexate is a toxic medication and that it is not administered on a mg/kg basis because of the risk of death. That is not true. Methotrexate is administered for cancer treatment on the basis of body surface area not mg/kg because that is the dosage method that has been used in cancer treatment efficacy studies. It was a method developed for cancer clinical trial design decades ago and as discussed in a paper in the published literature in 1998, the use of the body surface area instead of body weight for dosing was merely to assist in design of phase I clinical studies for anticancer agents (see Ratain, M.J. 1998. *J. Clin. Oncol.* 16:2297-2298). In the 1998 paper, the physician states that the use of body surface area is not science based and related strictly to anything such as toxicity potential but has become instead myth handed down through generations. Therefore, contrary to the Examiner's suggestion, the use of mg/kg for methotrexate is not inappropriate for pain treatment as claimed.

Although use of body surface area dosing is routine in oncology it is NOT ROUTINE in pain therapy. In fact, the teaching of the specification as filed shows that a low dose of methotrexate has efficacy to treat pain when it is given intrathecally into the spinal cord.

Therefore, as discussed in the previous replies, although it is true that methotrexate is often dosed on a mg/m2 basis in cancer therapy, this is NOT the case for drugs used to treat pain. This is because, as taught only in the specification as filed, one of skill would need to understand how efficacy related to safety in any particular species. That is why the teaching of the specification as filed is clear in defining dose on a mg/kg basis, to allow one of skill to understand how to extrapolate doses across different species. Chamberlain et al., however, is silent on this issue and thus would not be used by one of skill to extrapolate from a 2 mg dose in humans, which they would understand to be a dose of approximately 0.029 mg/kg/day based on a 70 kg individual or 0.033 mg/kg/day based on a 60 kg individual, to a dose in a smaller animal such as a rat. The 2 mg dose of Chamberlain et al. is much lower than the dose range claimed in the instant invention and as such would

not be obvious to one of skill in the art. Again as well, it must be remembered that it is a general principle of pharmacology that you extrapolate doses across species based on mg/kg not mg alone and not on mg/m2 for pain treatment.

In order to establish a *prima facie* case of obviousness, three basic criteria must be met. MPEP 2143. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art must teach or suggest all claim limitations. Clearly the reference cited fails to teach or suggest the invention as claimed. The reference cited, in fact, teaches use of methotrexate to treat cancer NOT lower back pain with radiculopathy. Second, the paper teaches use of a much lower dose range and a different route of administration. Therefore, this reference fails to teach the limitations of the claim as amended and also fails to provide one of skill with an expectation of success. It is only with the specification in hand that one of skill would understand that intrathecal administration at a dose level of 1

mg/kg body weight would be effective for treating lower back pain with radiculopathy. Accordingly, this reference cannot make obvious the invention of the amended claim.

Respectfully submitted,

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